Attach. #5 IDS

INFORMATION DISCLOSURE STATEMENT

In accordance with their duty of disclosure under 37 C.F.R. §1.56, applicants would like to direct the Examiner's attention to the following documents which are listed on Form PTO-1449, attached hereto as **Exhibit E** and are also listed below. Copies of the documents listed below as items 1-33 are attached hereto as Exhibits 1-33, respectively.

1. U.S. Patent No. 5,766,842, issued June 16, 1998, Melnick, et al. **(Exhibit 1)**;

2. U.S. Patent No. 5,837,464; Capon, et al. issued November 17, 1998 "Compositions and Methods For Determining Anti-Viral Drug Susceptibility and Resistance and Anti-Viral Drug Screening" **(Exhibit 2)**;

3. International Search Report for the PCT Application No. PCT/US00/17178, filed June 22, 2000 with the U.S. Receiving Office **(Exhibit 3)**;

4. Dreyer GB, et al. (1993) "A Symmetric Inhibitor Binds HIV-I Protease Asymmetrically" Biochemistry **32**:937-947 **(Exhibit 4)**;

5. J. Eron, et al., (1995) Preliminary Assessment of 141W94 in Combination with Other Protease Inhibitors", 5th Conference on Retroviruses and Opportunistic Infections: 6 **(Exhibit 5)**

6. Hill, A. et al. (1998) "Low frequency of genotypic mutations associated with resistance to AZT and 3TC after combination treatment with indinavar", Int. Conf. AIDS **12:812**, (Abstract No. 42197) **(Exhibit 6)**;

7. E.E. Kim, (1995) " Crystal Structure of HIV-1 Protease in Complex with VX-478, a Potent and Orally Bioavailable Inhibitor of the Enzyme", J Am. Chem. Soc., 117: 1181-1182 **(Exhibit 7)**;

8. Lambert DM, et al. (1992) "Human Immunodeficiency Virus Type 1 Protease Inhibitors Irreversibly Block Infectivity of Purified Virions From Chronically Infected Cells" Anti Microb Agents Chem **36:**982-988 **(Exhibit 8)**;

9. Brendan A. Larder, et al., (1995) "Potential Mechanism for Sustained Antiretroviral Efficacy of AZT-3TC Combination Therapy", Science, 269; 696-699 **(Exhibit 9)**;

10. Janis K. Lazdins, et al., (1997) "In Vitro Effect of α_1-Acid Glycoprotein on the Anti-Human Immunodeficiency Virus (HIV) Activity of the Inhibitor CGP 61775: A Comparative Study with Other Relevant HIV Protease Inhibitors", J Infec. Dis., 175: 1063-1070 **(Exhibit 10)**;

11. David J. Livingston, et al., (1995) "Weak Binding of VX-478 to Human Plasma Proteins and Implications for Anti-Human Immunodeficiency Virus Therapy", J Infec. Dis., 172:1238-1245 **(Exhibit 11)**;

12. Bhuvaneshwari Mahalingam, et al., (1999) "Structural and Kinetic Analysis of Drug Resistant Mutants of HIV Protease", Biochem., 263: 1-9 **(Exhibit 12)**;

13. Miller M, et al. (1989) "Structure of Complex of Synthetic HIV-1 Protease with a Substrate-Based Inhibitor at 2.3 A Resolution" Science **246**:1149-1152 **(Exhibit 13)**;

14. Mohri H, et al. (1993) "Quantitation of Zidovudine-Resistant Human Immunodeficiency Virus Type 1 in the Blood of Treated and Untreated Patients", PNAS **90**:25-29 **(Exhibit 14)**;

15. Robert L. Murphy, et al., (1999) "Treatment with Amprenavir Alone or Amprenavir with Zidovudine and Lamivudine in Adults with Human Immunodeficiency Virus Infection" J. Infec. Dis., 179: 808-816 **(Exhibit 15)**;

16. Nájera I, et al. (1994) "Natural Occurrence of Drug Resistance Mutations in the Reverse Transcriptase of Human Immunodeficiency Virus Type 1 Isolates", Aids Res Hum Retroviruses **10**:1479-1488, **(Exhibit 16)**;

17. Nájera I, et al. (1995) "Pol Gene Quasispecies of Human Immunodeficiency Virus: Mutations Associated with Drug Resistance in Virus From Patients Undergoing No Drug Therapy", J Virol **69**:23-31, **(Exhibit 17)**;

18. Sarah Palmer, et al., (1999) "Highly Drug-resistant HIV-1 Clinical Isolates Are Cross-resistant to Many Antiretroviral Compounds in Current Clinical Development", AIDS, 13: 661-667 **(Exhibit 18)**;

19. Neil T. Parkin, et al., (1999) "Phenotypic changes in Drug Susceptibility Associated with Failure of Human Immunodeficiency Virus Type 1 (HIV-1) Triple Combination Therapy", J Infec. Dis., 180: 865-870 **(Exhibit 19)**;

20. Judith A. Partaledis, et al., (1995) "In Vitro Selection and Characterization of Human Immunodeficiency Virus Type 1 (HIV-1) Isolates with Reduced Sensitivity to Hydroxyethylamino Sulfonamide Inhibitors of HIV-1 Aspartyl Protease", Journal of Virology, 69: 5228-5235 **(Exhibit 20)**;

21. A. K. Patick, et al., (1998) "Genotypic and Phenotypic Characterization of Human Immunodeficiency Virus Type 1 Variants Isolated from Patients Treated with the Protease Inhibitor Nelfinavir", Antimicrobial Agents and Chemotherapy, 42: 2637-2644 **(Exhibit 21)**;

22. Petit SC, et al. (1993) "The Specificity of the HIV-1 Protease" Drug Discov Des **1:**69-83 **(Exhibit 22)**;

23. Roberts NA, et al. (1990) "Rational Design of Peptide-Based HIV Proteinase" Science **248:**358-361 **(Exhibit 23)**;

24. Roberts, N. A., (1995) "Drug-resistance patterns of saquinavir and other HIV proteinase inhibitors", AIDS.**9** (supp 2) S27-S32 **(Exhibit 24)**;

25. Brian M. Sadler, et al., (1999) "Safety and Pharmacokinetics of Amprenavir (141W94), a Human Immunodeficiency Virus (HIV) Type 1 Protease Inhibitor, Following Oral Administration of Single Doses to HIV-Infected Adults", Antimicrobial Agents and Chemotherapy, 43: 1686-1692 **(Exhibit 25)**;

26. Sarkar G. and Sommer SS., (1990) "The "Megaprimer" Method of Site-Directed Mutagenesis", BioTech **8(4)**:404-407 **(Exhibit 26)**;

27. Mary L. Smidt, et al., (1996) "A Mutation in Human Immunodeficiency Virus Type 1 Protease at Position 88, Located Outside the Active Site, Confers Resistance to the Hydroxyethylurea Inhibitor SC-55389A", Antimicrobial Agents and Chemotherapy, 41: 515-522 **(Exhibit 27)**;

28. M. H. St. Clair, et al., (1996) "In Vitro Antiviral Activity of 141W94 (VX-478) in Combination with Other Antiretroviral Agents", Antiviral Research 29: 53-56 **(Exhibit 28)**;

29. H. Tian, et al., (1998) "Zidovudine/Lamivudine Co-resistance Is Preceded by a Transient Period of Zidovudine Hypersensitivity", 2nd International Workshop on HIV Drug Resistance and Treatment Strategies, Abstract 30: **(Exhibit 29)**;

30. Tisdale, M. et al. (1998): "Genotypic and phenotypic analysis of HIV from patients on ZDV/3TC/amprenavir therapy", Int. Conf AIDS **12**:583 (Abstract No. 32312) **(Exhibit 30)**;

31. Simon P. Tucker, et al., (1998) "Estimate of the Frequency of Human Immunodeficiency Virus Type 1 Protease Inhibitor Resistance Within Unselected Virus Populations In Vitro", Antimicrobial Agents and Chemotherapy, 42: 478-480 **(Exhibit 31)**;

32. Young, B. et al., (1998) "Resistance mutations in protease and reverse transcriptase genes of human immunodeficiency virus type 1 isolates from patients with combination antiretroviral therapy failure. J. Infectious Disease, **178**: 1497-1501 **(Exhibit 32)**; and

33. Rainer Ziermann, et al., (in press May 2000) "A Mutation in HIV-1 Protease, N-88S, that Causes In Vitro Hypersensitivity to Amprenavir", J. Virol., 74: 4414-4419 **(Exhibit 33)**.

Applicants request that the Examiner review the references and make them of record in the subject-application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the $55.00 fee for a one-month extension of time is deemed necessary in connection with the filing of this Amendment and Information Disclosure Statement. However, if any other fees are required, authorization is hereby given to charge the amount of such fees to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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